Heparin Treatment for Pregnant Women with Protein S Deficiency: A Systematic Review

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Research Question

For pregnant women with thrombophilia disorders, how does the use of heparin compared to those who do not receive heparin influence the risk of developing adverse pregnancy outcomes, with a greater emphasis on Protein S deficiency?

Introduction

- The deficiency of Protein S (PS), a clotting factor that regulates blood coagulation, causes an increased risk of blood clotting due to a variation in the *PROS1* gene.
- PS deficiency is one of many inherited hypercoagulable conditions.
- There are life threatening risks of developing blood clots from these inheritable thrombophilia, including pulmonary embolisms and deep vein thromboses, however many individuals with Protein S deficiency never experience complications.
- Warfarin is an anticoagulating drug that has been used in clinical settings for over 50 years to reduce blood clots, but its use during pregnancy is heavily linked to stillbirth, spontaneous abortion, neonatal death, premature delivery and a variety of congenital anomalies known as fetal warfarin syndrome (FWS)

Methods

- PubMed and CINAHL databases were searched in fall 2021 using the keywords: ((protein s deficiency[Title/Abstract]) AND (heparin[Title/Abstract] OR enoxaparin[Title/Abstract])) AND (pregnancy[Title/Abstract])
- The search was limited to studies pertaining to pregnant women with Protein S deficiency who were treated with heparin.
- Three Protein S deficient Specific articles that included PS deficient patients were identified and included in this review, and additional four that included PS deficient patients

Table 1. Summary of Studies Reviewed

Source	Context	Design	Intervention	Results
Bar et al. (2000)[1]	Petah Tikvah, Israel 65 patients, 22 with Protein S deficiency, 14-24 weeks gestation with 3 or more miscarriages, intrauterine growth restriction (IUGR), and preeclampsia between October 1996 and October 1998.	Randomized control trial testing effectiveness of low-dose aspirin plus low molecular weight heparin (LMWH) or low-dose aspirin on fetal and maternal Doppler flow parameters.	Those with a thrombophilia received 100mg/day of low-dose aspirin and 40mg/day of enoxaparin. The other patients received only low-dose aspirin.	The group receiving LMWH showed no significant change (P>0.5) compared to control group in maternal and perinatal outcomes (preeclampsia, caesarean section, gestational week of delivery, birth weight, IUGR, neonatal hospitalization rate) however they did show a significant decrease (P=.006) in uterine artery pulsatility index (PI) while those given aspirin had nonsignificant changes.
De Vries et al. (2012)[2]	The Netherlands, Australia, Sweden 128 subjects, 24 with Protein S deficiency, a history of uteroplacental insufficiency, HD, and chronic hypertension between December 2000 and December 2009.	Multicenter randomized control trial to test whether adding LMWH to aspirin before 12 weeks into the pregnancy decreases the recurrence of hypertensive disorders (HD).	Subjects were randomized to receive either 5000IU of dalteparin with 80mg aspirin daily or just 80mg aspirin daily. Dalteparin was adjusted based on weight.	LMWH with aspirin decreased recurrence of HD before 34 weeks gestation (P=0.012). There were no significant difference between the groups for secondary outcomes (gestational weight, abortion, pre-eclampsia, HELLP syndrome, and side effects).
Gris et al. (2004)[3]	Languedoc-Roussillon Region, France 160 patients with ≥ 1 pregnancy loss, 28 with PS deficiency.	Prospective evaluation comparing aspirin with enoxaparin to improve live birth outcomes.	Patients were given 100mg daily of low-dose aspirin or 40mg daily of enoxaparin.	Enoxaparin group had higher live birth rates than aspirin (P=0.0006) for PS deficiency specifically. The population showed a higher neonate weight for those treated with enoxaparin than in the aspirin group (P=0.0005).
Grünewald et al. (2021)[4]	Heidenheim, Germany 74 pregnancies, 6 with PS deficiency from 2009 to 2019.	Single center, retrospective, observational trial observing those receiving certoparin.	Study observed 74 pregnancies receiving a dose of 8,000 IU of certoparin daily.	Certoparin was determined effective in preventing thromboembolism and reducing spontaneous abortion rates. No P-Values Available.
Riyazi et al. (1998)[5] **Preliminary study to De Vries et al.**	Amsterdam, The Netherlands 26 patients (18 Protein S deficient) found with previous pregnancy, coagulation abnormalities, and preeclampsia or isolated fetal growth restriction were tested between January 1993 and January 1996.	Preliminary study to evaluate the effects of LMWH and aspirin on pregnancy outcome for women with homeostatic abnormalities. Those with abnormalities were compared to those without abnormalities but had similar pregnancy outcomes. Those without abnormalities received only aspirin.	26 women were treated with heparin or aspirin.	38% patients with abnormalities and 32% without abnormalities had preeclampsia. None had abruptio placenta. Birth weights for Protein S deficient and protein C deficient patients were significantly higher when treated with heparin than those who were treated with aspirin. (0.019).
Shen et al. (2016)[6]	Taiwan 50 women with PS deficiency and recurrent pregnancy loss (RPL) between 2011-2016.	Historical control cohort study to determine effect of LMWH on live birth rates.	Patients who lost a pregnancy while receiving low-dose aspirin then received 1mg/Kg or enoxaparin every 12 hours from beginning of enrollment to a few days before their next birth.	There were 47 successful livebirths. 12 had successful livebirths with aspirin, and with the following second pregnancies, only 3 resulted in abortion (due to aneuploidy pregnancy). No P-Values Available.
Shinozaki et al. (2016)[7]	Kobe, Japan 38 women with PS deficiency and RPL between June 2009 and March 2014.	Prospective study to compare aspirin with unfractionated heparin to determine effect on birth week, birth weight, and pregnancy complications (fetal growth restriction, pregnancy induced hypertension, preterm delivery)	Patients either received 81mg of aspirin daily until 27 gestational weeks (GW) or 5,000-10,000 units of unfractionated heparin daily until 36 GW.	For those without a PL and only PS deficiency, there was reportedly no significant difference (no p-value provided) between those who received aspirin and those receiving LMWH.

Results

- Primary sources include a prospective evaluation study, a historical cohort study, and a prospective study
- Non-specific studies studies included a randomized control trial, a multicenter randomized control trial, a retrospective, observational trial, and a preliminary study
- Most research advocates for the use of heparin during pregnancy for those with Protein S deficiency and other thrombophilia
- One study showed no significant difference when compared to aspirin as an intervention.
- In all but one study, heparin interventions resulted in at least one positive outcome for both mother and child, including uterine artery pulsatility index, recurrence of HD, live birth rate, neonate weight, and thromboembolism prevention

Conclusion

- Heparin is promising as an intervention for PS deficiency and other thrombophilia in pregnant women.
- Heparin interventions and other interventions need further research to explore treatment options that protect both mother and fetus in hypercoagulable states.

References

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